Invention Summary

The invention disclosed in US 09/931,883 relates to a method to detect DNA structure-specific binding proteins while bound to an immobilized DNA substrate. The method also relates to the identification of modulators of DNA structure-specific binding proteins which could be pharmaceutically relevant compounds.

Specific Responses to Detailed Action

My responses to the Action have been numbered to correspond to those paragraphs numbered in the Action.

1. I acknowledge the withdrawal of restriction requirements, and appreciate this action be the office.
2. I have enclosed (PTO/SB/08) as an information disclosure statement.
3. ***Claim Rejections – 35 USC § 112***
4. I have amended claims 1-22 to more distinctly claim the embodiments of the invention, with details described below for each specific concern described by the examiner, and changes noted in the "Claim Amendments" sections above. Claims 3 and 15 were deleted because the term "nucleic acid" was replaced with "DNA" in Claims 1 and 12. Claim 13 was canceled because the detection step was incorporated into claim 12. A new claim (claim 23) was added to cover the embodiments of the original claim 12.
5. I have changed "the DNA" to "DNA", and "a method" to "A method" in Claim 1. Additionally, Claim 1 was amended to clarify that the detection of the test protein is done while the nucleic acid substrate is still immobilized (see claim amendments).
6. In Claim 9, I have replaced "the DSSBP" with "test protein" to maintain consistency within the claim set.
7. I have significantly amended claim 12 to clarify the invention (Amended Claim 11, see Claim Amendments). With regards to lack of antecedent basis, the term "the DSSBP" was replaced with "DNA structure specific binding protein". As mentioned, the detection step was included as part (c) in claim 12.
8. I have removed "capable of" in Claim 12.
9. I have added period to Claim 12.

10. I have canceled Claim 13, and modified Claim 12 to include the detection step. In this regard, Claim 12 has also been modified to clarify that the detection of the DNA structure-specific binding protein is done while the nucleic acid substrate is still immobilized (see Claim Amendments).

11. Claim 22 is indeed dependent on claim 19 (Amended Claim17), and this typo has been corrected in the "Claim Amendments".

12. ***Claim Rejections – 35 USC § 102***

13. I have modified Claim 1 to clarify that the immobilized DNA is still bound to the solid phase during the detection step. This is significantly different than that of Crute (US Pat. 5,958,696) who detects DNA *released* from the solid phase by the helicase. Additionally, the present invention detects *protein* bound to DNA, not the DNA itself as in Crute.

14. I believe the present invention is significantly different than Giordano et al. (US Pat. 5,705,344) wherein detection of helicase activity is done *indirectly* by detecting a nucleic acid retained on a solid-support. In the present invention, detection of a DNA structure-specific binding protein bound to an immobilized nucleic acid is accomplished while the protein-DNA interaction occurs on the solid phase. In this regard, I have modified Claim 1 to clarify that the DNA is still bound to the solid phase during the protein detection step.

15. Shi et al. (US Pat. 5,919,626) describe detection of a nucleic acid capable of hybridizing to a second nucleic acid on a solid support. The present invention is unique in that a *protein* is detected bound to an immobilized nucleic acid. Thus, the "polynucleotide analyte" of Shi et al. does not apply to the present invention, and a "DNA structure-specific binding protein" of the present invention is not applicable to Shi et al.

16. With regards to Yamane et al. (US Pat. 5,741,638) the present invention is novel in that it discloses a *protein* being detected bound to an immobilized nucleic acid, whereas Yamane discloses detection of a *nucleic acid* by hybridization. In their indirect method, as mentioned by the examiner, an antibody (which is a protein) may be used as a detection acceptor. However, in this method the detection scheme is done to detect presence of nucleic acid hybridization, not detection of a protein-DNA complex. In Yamane (Col. 6, line 35) the binding process can be conducted simultaneously with the hybridization (i.e. the antibody-nucleic acid complex can be added to the solid phase directly). In this regard I have added the word "then" to Claims 1 to denote the stepwise fashion of the present invention. Furthermore, in Yamane, when using an antibody to detect hybridization, three components are needed: (i) a single-stranded nucleic acid bound to a solid support, (ii) a second nucleic acid which can hybridize to the first, and (iii) a detection mechanism (which can be an antibody). The present invention only requires: (i) a DNA molecule comprising a structure, and (ii) a protein capable of binding this DNA. In this regard, I

note the amendments to Claim 1 and Claim 12 wherein the word "single" is included to denote that only one DNA molecule is necessary in step (a).

17. Mitsuhashi (US Pat. 5,639,612) also described mechanisms to detect nucleic acids by hybridization. With regards to Mitsuhashi the arguments and Claim amendments described above in relation to Yamane also apply.

18. **Claim Rejections 35 USC § 103**

19. I believe the present invention is non-obvious for the reasons described in 20 below.

20. Giordano teaches a screen for helicase inhibitors, wherein DNA bound to a solid support is detected as an indirect measure of helicase activity. The present invention detects a protein bound to immobilized DNA. As mentioned, I have modified Claim 1 and Claim 12 (Amended Claim 11) to indicate that the detection of the protein occurs while the nucleic acid is still immobilized. This detection method would be impossible in the invention disclosed in Giordano, because the helicase in their invention does not bind to the DNA to any significance which would allow it to be detected. Because the helicase is not bound to the solid support, it cannot be detected with *any* antibody. Thus, use of an anti-DNA-PK antibody in their system would also be impossible as a means of detection. Therefore, use of DNA-PK or an anti-DNA-PK antibody (as in the present invention Amended Claims 9-10 and 19-20) are not obvious since they could not be used in Giordano et al.

For the above reasons, I submit that the claims, as amended, are patentable and should be passed to issuance.

Vaughn Smider